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Treatment of IgA nephropathy

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IgA nephropathy (IgAN) is an important cause of progressive kidney disease with 25–30% of patients developing end-stage renal disease within 20 years of diagnosis. There is still no treatment to modify mesangial IgA deposition and available treatments are those extrapolated from the management of other patterns of chronic glomerulonephritis. There remains no consensus on the use of immunosuppressive agents for treatment of progressive IgAN and this is compounded by the relative lack in IgAN of randomized controlled trials relevant to current clinical practice. Patients with recurrent macroscopic hematuria or isolated microscopic hematuria and proteinuria <1 g/24 h require no specific treatment. Those with nephrotic syndrome and minimal change on renal biopsy should be managed as for minimal change nephropathy. There is no evidence to support the use of corticosteroids for nephrotic IgAN outside this group of patients. Patients presenting with acute renal failure require evaluation to distinguish acute tubular necrosis, which requires supportive therapy only, from crescentic IgAN, for which treatment with cyclophosphamide and corticosteroids in a regimen similar to that for renal small vessel vasculitis is indicated in the absence of significant chronic histologic injury. Patients at greatest risk of progressive renal impairment are those with hypertension, proteinuria >1 g/24 h, and reduced glomerular filtration rate at diagnosis. All such patients should be treated to a blood pressure of 125/75 mm Hg with dual blockade of the renin–angiotensin system with angiotensin-converting enzyme inhibition and angiotensin receptor blockade. At present, there is insufficient evidence for the additional use of immunosuppressive agents, antiplatelet agents, or anticoagulants.

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Immunoglobulin A nephropathy (IgAN) is the most common pattern of idiopathic glomerulonephritis in all countries where renal biopsy is widely practiced. It is an important cause of end-stage renal disease (ESRD) at all ages, and therefore treatment strategies to reduce the risk of IgAN progressing to ESRD would have substantial health benefit. There are, however, few well-designed randomized controlled trials (RCTs) to inform the treatment of this condition. The reason for this is in part the slow rate of progression of IgAN, making it necessary to study large numbers of patients for prolonged periods of time to determine the efficacy of any therapeutic intervention. Another consequence of the slowly progressive nature of IgAN is that for many of the trials now published patient recruitment occurred at a time when the management of progressive glomerular disease was less clearly defined than it is now.

In this review, we will critically evaluate the available evidence on the treatment of IgAN, especially focusing on recently published RCTs; earlier available data have been reviewed elsewhere.[1] We will also provide recommendations for the common clinical situations that confront the nephrologist treating patients with IgAN.

CLINICAL PRESENTATIONS AND DIAGNOSIS

Asymptomatic urine abnormalities, microscopic hematuria with or without proteinuria, are a common presentation and with increasing age these features are more likely to be accompanied by renal impairment and hypertension when first seen. The typical presentation of macroscopic hematuria following a mucosal (usually upper respiratory) infection is most common in the second and third decades of life and is almost never the presenting symptom after the age of 40 years. Nephrotic syndrome occurs in around 5% of cases. Acute renal failure may result from acute tubular necrosis as a consequence of macroscopic hematuria or superimposed crescentic nephritis and is seen during the course of the disease in <5% of cases.

Renal biopsy confirms the diagnostic feature of diffuse mesangial IgA deposition with a wide range of light microscopic appearances, although diffuse or segmental mesangial proliferation is the most common.

NATURAL HISTORY AND PROGNOSIS

Resolution of urinary abnormalities occurs in less than 10% of all patients. More commonly, IgAN is associated with

slowly progressive chronic renal impairment with between 25 and 30% of any cohort developing ESRD within 20–25 years of presentation. Local variations in the perceived risk of ESRD in IgAN stem primarily from the different diagnostic approaches adopted internationally. Centers with a low threshold for renal biopsy for patients with mild urine abnormality, particularly in countries with active urine screening programs, are more likely to diagnose mild disease with good prognosis, thus favorably influencing the overall outcome of the cohort.

Adverse clinical features at presentation include proteinuria, hypertension, and reduced glomerular filtration rate (GFR), and adverse histopathologic features include glomerular sclerosis, tubular atrophy, and interstitial fibrosis.[2] None of the features that mark a poor prognosis are specific to IgAN, and would be applicable to any form of chronic proteinuric glomerular disease. They are informative for populations of patients, but as yet do not have the specificity to identify an individual prognosis with complete confidence. An approach incorporating sequential information on blood pressure (BP) and proteinuria can further refine the prediction of progression risk, although this will still only account for 30% of overall risk. Although prognostic formulae using simple clinical and laboratory data have been proposed, there is not yet sufficient consensus to recommend their use in clinical practice for the prediction of individual progression risk. It also remains uncertain whether pathological classification adds to predictive power in the individual patient; progress in defining the answer has been limited by the lack of an international consensus on pathological classification of IgAN. Further refinement of prognostic prediction will inform recruitment criteria for future interventional treatment trials.

Recurrence of IgAN after renal transplantation is assuming increasing importance as a cause of graft failure as control of rejection improves. The diagnosis and management of recurrence have recently been reviewed in detail,[3] and we will not here consider this further.

TREATMENT STRATEGIES

There is still no treatment known to modify mesangial deposition of IgA. Available treatment options are mostly directed at downstream immune and inflammatory events in the glomerulus and the tubulo-interstitium, which may lead on to renal scarring. It is therefore likely that these are generic treatments with potential benefit in other chronic glomerular diseases.

Here we will review the available treatments from the perspective of each clinical presentation encountered in IgAN; treatment recommendations are summarized in Table 1.

Recurrent macroscopic hematuria

Such episodes are self-limiting, and provoked by a range of mucosal, most commonly respiratory, infections. There is no role for prophylactic antibiotics, even in the minority of patients in whom recurrent episodes are provoked by bacterial tonsillitis. Tonsillectomy is still favored in some regions of the world, notably Japan. Tonsillectomy may help to prevent episodic macroscopic hematuria in the short term, and proponents of tonsillectomy argue that it also gives long-term renal protection. This view is supported by two large retrospective studies from Japan, although benefit was not apparent until 10 years after tonsillectomy.[4,5] The concomitant use of other treatment modalities and changing therapeutic goals during the follow-up period make these data difficult to interpret; a retrospective study from Germany suggests no benefit of tonsillectomy.[6] An RCT of tonsillectomy in IgAN is now being planned in Japan.

In our opinion, no specific treatment is required for patients with IgAN presenting with recurrent macroscopic hematuria and preserved GFR.

Table 1 | Treatment recommendations for IgAN according to clinical features

Clinical presentation	Recommended treatment
Recurrent macroscopic hematuria with preserved renal function	No specific treatment – no role for antibiotics or tonsillectomy
Proteinuria <1 g/24 h $\pm$ microscopic hematuria	No specific treatment
Proteinuria >1 g/24 h $\pm$ microscopic hematuria	Combined renin–angiotensin blockade with ACE inhibitor and ARB
Acute renal failure	
Acute tubular necrosis	Supportive measures
Crescentic IgAN (with little or no chronic damage)	
Induction ($\sim$8 weeks)	Prednisolone 0.5–1 mg/kg/day Cyclophosphamide 2 mg/kg/day
Maintenance	Prednisolone in reducing dosage Azathioprine 2.5 mg/kg/day
Nephrotic syndrome	
With minimal change on light microscopy	Prednisolone 0.5–1 mg/kg/day for up to 8 weeks
With structural glomerular changes	No specific treatment
Hypertension	Target BP 125/75 mm Hg if proteinuria >1 g/24 h ACE inhibitors/ARB first choice agents

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; IgAN, IgA nephropathy.

Isolated microscopic hematuria and little or no proteinuria

It is generally accepted that no specific treatment is required, although patients should receive regular follow-up. A threshold for proteinuria of 1 g/24 h is commonly used to identify those at increased risk of progression, although this is an arbitrary value, and the risk attributable to proteinuria is almost certainly a continuum.

Acute renal failure

Acute renal failure is an uncommon event in IgAN and most commonly occurs with macroscopic hematuria. Even if the diagnosis of IgAN has previously been established, evaluation should include renal biopsy unless renal function improves within 2–3 days of supportive treatment. The biopsy will distinguish between ARF owing to acute tubular necrosis, which should be self-limiting with continuing supportive treatment, and crescentic IgAN, which may be amenable to intensive immunosuppression (see below).

Crescentic IgAN

Crescentic IgAN has a less good prognosis despite immunosuppressive therapy than other forms of crescentic glomerulonephritis, for example, that associated with antineutrophil cytoplasmic antibody-positive small vessel vasculitis; cumulative published cases suggest that renal survival in crescentic IgAN is only 50% at 1 year and 20% at 5 years. A number of optimistic case series have recently been published indicating good preservation of renal function using treatment regimens similar to those recommended for renal vasculitis, usually with high-dose corticosteroids and cyclophosphamide, and in some cases, plasma exchange (reviewed by Tumlin and Hennigar[7]). However there has still been no RCT of these treatments in crescentic IgAN, and response to treatment is not uniform. There is a lack of clarity because published reports use varying definitions of crescentic IgAN, for example, some include cases where crescents are seen, but other acute injury to the glomerular tuft is not intense and renal function is not deteriorating. One report indicates that there is a subset of crescentic IgAN with circulating antineutrophil cytoplasmic antibodies, which respond well to immunosuppression.[8] Crescentic IgAN may occur as the first presentation of IgAN with little preceding renal insult; on the other hand, it is not uncommon to see crescentic change on a background of chronic glomerular and tubulointerstitial injury; such chronicity usually predicts a poor response to intensive immunosuppression.

We only recommend immunosuppressive treatment with cyclophosphamide and corticosteroids when crescentic IgAN ($>10\%$ of glomeruli affected by crescents) is associated with active glomerular inflammation and deteriorating renal function in the absence of significant chronic damage (Table 1).

Nephrotic syndrome in IgAN

In many patients with IgAN and nephrotic syndrome, the heavy proteinuria is a manifestation of significant structural glomerular damage and progressive renal dysfunction. However, a small minority, both adults and children, have nephrosis with minimal glomerular change on renal biopsy, although there are also IgA deposits, and proteinuria remits promptly in response to corticosteroids. In these patients, two common glomerular diseases may coincide: minimal-change nephrotic syndrome and IgAN.[9,10] This observation justifies a trial of high-dose corticosteroids using a regimen appropriate for minimal-change disease in IgAN with nephrotic syndrome and preserved renal function when light microscopy shows minimal glomerular injury. However, there is no evidence to support prolonged exposure to corticosteroids if there is neither a prompt response nor their use in nephrotic syndrome in the presence of structural glomerular damage. The only RCT of corticosteroids in nephrotic IgAN confirms this approach as there was remission of proteinuria only in patients with minimal glomerular change on light microscopy.[11] More recent RCTs of corticosteroids in IgAN have excluded those with nephrotic-range proteinuria, so there is little evidence to inform treatment choices for nephrotic IgAN with significant histologic glomerular injury.

Other than patients with IgAN and histological features of minimal change, we do not recommend the use of corticosteroids for the treatment of nephrotic syndrome in IgAN.

Slowly progressive IgAN

Patients at risk of progressive renal dysfunction are typically those with hypertension, proteinuria >1 g/24 h, or reduced GFR at the time of diagnosis. Specific treatment strategies in this group of patients remain contentious. Progression is usually slow and therefore large studies with prolonged follow-up are necessary to evaluate new treatment strategies in these patients. Unfortunately, many of the published studies in progressive IgAN have been insufficiently powered and consequently no definitive conclusions on treatment options can be made. Also, all trials in IgAN use clinical entry criteria – typically the presence of hypertension and proteinuria 1–3 g/24 h, with variable reduction in GFR. This is in contrast, for example, to studies in lupus nephritis where histological criteria usually dominate recruitment, and reflects the lack of international consensus on a histopathological classification of IgAN.

BP control. The recommended approach to proteinuric patients with glomerular disease emphasizes rigorous BP control to a target of 125/75 mm Hg with maximal renin–angiotensin system blockade to minimize proteinuria.[12] There is some specific evidence in IgAN to justify tight BP control: in one small RCT, achieved mean BP of 129/70 mm Hg stabilized GFR over 3 years, whereas patients with achieved BP of 136/76 mm Hg showed a mean decline in GFR of 13 ml/min over 3 years.[13] Another small RCT supports the additional benefit of an angiotensin-converting enzyme inhibitor on progressive renal disease in IgAN despite equivalent BP control by achieving an additional reduction

in proteinuria.[14] Furthermore, the COOPERATE study provides evidence for additive renoprotection when an angiotensin receptor blocker is given in combination with an angiotensin-converting enzyme inhibitor in non-diabetic proteinuric renal disease; additional reduction in proteinuria being achieved with no further lowering of BP; 131 of the patients in this large study had IgAN.[15]

Treatments modulating immune and inflammatory injury. Recently reported RCTs have tested interventions intended to slow immune and inflammatory events implicated in progressive IgAN including corticosteroids, cyclophosphamide, and mycophenolate mofetil. Because of the long duration required to identify with confidence the benefit of interventions, it is inevitable that recruitment into a number of these studies goes back 10 years or more, to a time when the generic approach to progressive glomerular disease was less well defined, so that BP targets and the use of renin–angiotensin blockade are variable in these studies.

Corticosteroids: Six trials (341 patients) were considered of sufficient quality to be included in a recent meta-analysis of immunosuppressive treatments for IgAN.[16] This analysis suggests that corticosteroid therapy may be effective in reducing proteinuria and reducing risk of ESRD. Follow-up in the large Italian study of corticosteroids has now reached 10 years and reports impressive benefit from treatment in reducing proteinuria and preventing ESRD.[17] However, their high-dose corticosteroid regimen, using 'pulse' methylprednisolone (1 g daily for 3 days at induction and beginning of months 2 and 4) and alternate day oral prednisolone (0.5 mg/kg) for 6 months, is regarded by many physicians as likely to carry considerable toxicity, even though none is reported by the investigators. Notably, renin–angiotensin system blockade was only used in a minority of patients in this study, although equally distributed among the participants, and achieved BP was not in line with current recommendations (Table 2). Another recent RCT of corticosteroids (20 mg/day induction; 5 mg/day maintenance) from Japan in which BP control was tight even though renin–angiotensin system blockade was not used (Table 2) showed only a modest reduction in proteinuria with no protection of GFR.[18] It is unclear whether this lack of renoprotection was owing to the lower dose of corticosteroid or a genuine lack of effect in patients managed to current BP targets.

In our view, corticosteroids should be considered only when there is continued proteinuria (>1 g/24 h) despite tight BP control ($<125/75$ mm Hg) and maximal renin–angiotensin system blockade.

Cyclophosphamide: The use of cyclophosphamide in patients at very high risk of progression (ESRD predicted in all cases within 5 years) is supported by a single study. Patients received cyclophosphamide (1.5 mg/kg/day for 3 months) followed by azathioprine (1.5 mg/kg/day) in conjunction with high-dose prednisolone (40 mg/day induction; 10 mg/day maintenance) and were followed for at least 2 years.[19] Notably, BP control and use of renin–angiotensin system blockade in this trial fell outside current recommendations (Table 2). Previous RCTs of cyclophosphamide in less severe IgAN showed no consistent benefit (reviewed by Feehally[1]).

In our opinion, there is insufficient evidence to support the use of cyclophosphamide in IgAN, except in crescentic IgAN with rapidly progressive renal failure (see above).

Mycophenolate mofetil: Two studies report no benefit from mycophenolate mofetil (2 g/day) in patients either at risk of progression (hypertensive and/or proteinuria >1 g/24 h and/or reduced GFR within 5 years of diagnosis)[20] or with more advanced disease (mean serum creatinine at entry 2.6 mg/dl).[21] Both of these studies achieved rigorous BP control with use of an angiotensin-converting enzyme inhibitor (Table 2). In two separate studies, mycophenolate mofetil (1–2 g/day) did reduce proteinuria over an 18-month follow-up period; however, neither study demonstrated a change in rate of renal decline.[22,23] Again both studies achieved tight BP control with angiotensin-converting enzyme inhibition. The relatively small size and short duration of the studies so far available justifies further evaluation, and other studies are in progress.[24]

Table 2 | Treatment of IgAN and achieved BP and use of renin–angiotensin blockade in recently published RCTs

Treatment	Benefit	Achieved BP (mm Hg)	ACE inhibitor or ARB
ACE inhibitor ± ARB[15]	Reduction in proteinuria and preserved GFR; best with ACE inhibitor plus ARB	125/70	ACE inhibitor or ARB or combination
Corticosteroids[17]	Reduction in proteinuria and reduced ESRD at 10 years	134/84	43% – used equally in both study groups
Corticosteroids[18]	Small reduction in proteinuria; no effect on GFR	125/80	8% – most used in responders
Corticosteroids+ cyclophosphamide[19]	Renoprotection in very high risk patients	145/85	Unclear
Mycophenolate mofetil[20]	None	125/73	100%
Mycophenolate mofetil[21]	None	129/81	100%
Mycophenolate mofetil[22]	Reduction in proteinuria; no effect on GFR	Uncertain	None
Mycophenolate mofetil[23]	Reduction in proteinuria; no effect on GFR	122/71	100%

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; ESRD, end-stage renal disease; GFR, glomerular filtration rate; IgAN, IgA nephropathy; RCT, randomised controlled trial.

In our opinion, there is insufficient evidence at present for the use of mycophenolate mofetil for the treatment of progressive IgAN.

Fish oil: The initial study of fish oil in IgAN reported significant benefit in patients at risk of progression;[25] however, there are still no further studies to support its role, and a meta-analysis including other published studies does not suggest efficacy.[26] The preliminary report of a more recent RCT shows no benefit following 2 years treatment with fish oil compared to corticosteroids and placebo.[27]

On the available evidence, we do not recommend the use of fish oil.

Coagulation modifying agents: Warfarin, urokinase, and antiplatelet agents have all been assessed for the treatment of IgAN. The earlier trials of these agents have been reviewed elsewhere.[1]

In our opinion, there is at the present time insufficient evidence to support the use of warfarin, urokinase, or antiplatelet agents.

Choice of therapy

This remains a controversial area, but in our opinion adjunctive therapy with corticosteroids or other agents should only be considered in patients with sustained proteinuria >1 g/24 h despite achieving target BP of 125/75 mm Hg with full renin–angiotensin blockade. In our clinical experience, there are few patients who fulfill these criteria, and it should be recognized that the efficacy of corticosteroids, cyclophosphamide, and mycophenolate mofetil has not been adequately evaluated by RCT in the context of such a 'standard regimen'. It should also be noted in Table 2 that those studies in which contemporary BP targets were achieved and full renin–angiotensin blockade deployed were those least likely to show benefit from the additional therapy.

Furthermore, the recently published meta-analysis of immunosuppressive treatments for IgAN, which suggested benefit for corticosteroids and immunosuppressive agents, was unable to include complete data on achieved BP or the use of renin–angiotensin blockade and so the possibility that these were confounding factors could not be evaluated.[16]

FUTURE PROGRESS

It is unfortunately becoming increasingly difficult to judge the efficacy of any proposed new therapeutic intervention. The renoprotective efficacy of the 'standard regimen' means that evaluation of any additional intervention will require increasingly large and prolonged RCTs to prove benefit for additional agents unless robust surrogate measures of outcome are developed to enable studies to be scaled down without loss of power. Information from well-designed RCTs remains a pressing priority if uncertainties in the treatment of IgAN are to be resolved.

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